Micobiome

Transcript

[Upbeat theme music plays]

Dr. Clancy

Welcome to Rounding@Iowa, a continuing medical education podcast developed by and for healthcare teams. I'm your host, Dr. Jerry Clancy, Senior Associate Dean of External Affairs for the Carver College of Medicine here at the University of Iowa. There is certainly new interest in healthy foods from health leadership at both the federal and state level. This past year, the Iowa legislature passed a law requiring additional training for physicians on nutrition to maintain our medical license. Today, we'll delve into an increasingly important topic in relation to nutrition and disease. We will discuss what we know about the microbiome, its relation to disease, and how we can promote a healthy microbiome. At the conclusion of this activity, participants should be able to, first, Describe the normal physiology of the gut and oral microbiome, including its roles in immune regulation, metabolism, and brain signaling, and how these functions support health overall. Second, recognize clinical conditions associated with microbiome dysregulation and distinguish where current evidence supports a contributory or causal role versus emerging or speculative associations. And third, apply evidence-based dietary and lifestyle strategies that promote a healthier gut and oral microbiome in clinical practice, including appropriate counseling on diet, antibiotics, and commercially available microbiome-related interventions.

Our first guest today is Dr. Sukirth Ganesan, a clinician scientist at the University of Iowa. He is a Centennial Research Associate Professor, the Director of Clinical Research, and the Director of the Advanced Education Program in Periodontics at the University of Iowa's College of Dentistry. His education and training background include a Master's in Public Health in Health Policy and Administration from the University of Illinois College of Public Health in Chicago, a dental clinical research fellowship in oral immunobiology from the National Institute of Dental and Craniofacial Research in Bethesda. He earned a PhD in oral biology and a certificate in periodontics from the Ohio State University College of Dentistry, and a Bachelor of Dental Surgery from the Tamil Nadu Medical University in India. His work focuses on the role of the gut and oral microbiome in human health and disease, Dr. Ganesan brings a clinician's perspective to microbiome science with particular interest in how microbial host interactions influence inflammation, metabolism, and disease risk.

We're delighted to have Dr. Ganesan here to help us translate this rapidly evolving science into practical insights for generalist physicians.

Our second guest is Dr. Ashu Mangalam, a professor in the Department of Pathology here at the University of Iowa Carver College of Medicine. He is the director of the University of Iowa Microbiome Core. His education and training background include a bachelor's in science in biology from Lucknow University in India, a master's in science in biotechnology from Devi Ahilya University, Indore, India, and a PhD in immunology from Sanjay Gandhi Postgraduate Institute of Medical Sciences. This was followed then by a postdoctoral fellowship in the Department of Immunology at Mayo Clinic. Dr. Mangalam is globally recognized for research exploring better treatment options to cure multiple sclerosis. In addition, he studies how the gut microbiome shapes immune responses and contributes to chronic inflammatory and immune-mediated diseases. His work has helped clarify key mechanisms linking microbial composition to disease pathophysiology, making him an ideal voice for our discussion today. He was recently recognized as a top five microbiome researcher. To both of you, thanks for taking the time to be with us today and thank you for being a guest on Rounding@Iowa.

Dr. Ganesan

Thank you very much for inviting us. Much appreciate it.

Dr. Mangalam

Thanks. It is a real pleasure to be part of this conversation as gut microbiome is something I loved and I'm happy to talk more about it.

Dr. Clancy

Well, it's great to have both of you on this increasingly important and interesting and public aware topic. Let's start with questions that really help set the stage for a deeper discussion on the microbiome. To start broadly, when clinicians hear the term gut microbiome or oral microbiome, what exactly are we talking about physiologically?

Dr. Ganesan

Great. I'm a dentist scientist, so I'm going to talk about oral microbiome a little bit. We have Ashu here who can talk a little bit more about the gut microbiome. So dentist, when we hear the word oral microbiome, I think things have changed a lot. That's how the way we talk about microbiome or our gut is has evolved over the years. initially bacteria means bad, pathogens. You got to make sure you kill them with antibiotics, right? That's how we always think about it. But things have evolved so much to understand that it's almost kind of a super organ, you know, so it's that you're living with it and there are different parts of

the body and there are different areas in the body where the microbiome exists from all the way from the skin surface to all the different inner tissue mucosal surfaces. When we talk about the word microbiome now, we think about it as a community that's existing in the body. And now more and more of understanding that it's important to keep the community in balance with our homeostasis and our environment. So I don't think we have any more of a it's good or a bad thought process when you hear the word. It's more of how does it contribute and how can we leverage the activities of the microbiome to make sure we think about the oral health. In oral health, we talk about periodontal disease or gum disease and cavities or dental caries or even oral cancer. Like all these three major conditions of the oral health or oral diseases, they all or have significant intricate relationship with the microbiome. So as a clinician, when I hear the word microbiome, I no longer get the red flag. I think about, take a pause and think about it and say, I need to understand what exactly is going on here. So that's my take as a dentist.

Dr. Mangalam

So I will just add on that. I think that's a good setup from the clinical perspective, and I will give more from the basic science perspective. So when we say microbiome, Sukirth mentioned it is a community structure where bacteria, fungi, viruses, and whatever comes next, prion and other, which reside primarily in this community. So microbiome is a term which we have inside our body or outside, but the maximum density is in the colon, almost trillions of microbes living there. And sometimes its numbers can be debated, but it seems either there are equal number or more number of these microbes in our gut than we have total number of cells in our body. So you can think about that we have evolved as a human. So you can think about this human as a machine, which we have our host cells as well as we have a microbe cells and their gene. And we work this as a holobiont system. So whatever we are going to discuss today, it's like Shakespeare quote, it is not I, it is the we what we do. And they do lots of things and they are very dynamic and we go and discuss They do multiple things. They digest food from us but educate immune system, maintain barriers, and produce lots of metabolites, signal every organ using best neurotransmitter. To put it simply, gut microbiome is a community of microorganisms which resides in and outside our body.

Dr. Clancy

Excellent. And I'm pretty sure I'm going to get over my head pretty quickly. So we've got two experts here. This was not taught in medical school when I went to medical school in the late 1980s. How is the understanding of the gut microbiome kind of evolved? When did it start and how rapidly is this field expanding as far as understanding?

Dr. Ganesan

When we talk about the microbiology, right, in our clinical training, I'm sure that they talk to us about the Cox postulates for pathogens, right? That's always taught to us in infectious diseases, in microbiology to say, how do you determine if something is a pathogen or not, right? So that was a lot of understanding. But interestingly, the way I think about the evolution is as the technological advances got more and more, I think we started understanding the microbiome more and more. And then one of the cool facts to add here is that the first time whenever the bacteria even was thought about do exist in the human body was when they actually looked it into the dental calculus and the plaque, right? That's what they swapped and looked at in the microscope. So that's when they realized, oh wow, okay, there is something moving here. And that looks like that's how the entire bacteriology, the microbiology, the field evolved. So once that thought process that the bacteria exist came in, then I think the revolution was, I would say, having the PCR, the polymerase chain reaction, when it came in the late 70s and 80s, correct me if I'm wrong, I'm sure, right? That's when the polymerase chain reaction came in, then we realized, oh, we could grow these a lot more. We actually look into this a lot more in detail. Then all of these different sequencing technologies came in, and those Sanger sequencing came in. Then pyrosequencing came in. You use on all different ways of understanding, or you just grow it on the well, and you actually pick one by one, each clone at a time, and actually go back and see and how what different kind of clones are growing on the plate. A lot of the times the restriction was what can grow is what was thought that is available. Then the PCR, then the uncultivated bacteria actually are almost 60% in the oral cavity. All those came in after the evolution of the PCRs. But the biggest evolution I want to say is the human microbiome project. When the Human Microbiome Project came in, I think that's when first people started realizing that, okay, these tiny bugs are the bacteria, as Ashu talked about, is in abundance, is in plenty. And the project also actually showed that the bacteria in the gut is very different from the bacteria in the oral cavity, and it's very different from on the skin, and that's on the urinary tract, and that's in your nasal cavity. It's all each of them. And that's when the concept of the niches came in. Like each individual niche has this individual bacterial communities. And a lot of these you can't just extrapolate, you know, just because, you know, even if in the same GI tract, the alimentary canal starts in the oral cavity. But just because I understand the oral microbiome, I can extrapolate the results to the gut. And it's the opposite. You need the same thing. You know, if I understand gut doesn't mean that I don't have to study oral cavity because all of these communities live by how does the environment in each of these changes, and if you think about the oral cavity, you are drinking, you're speaking, you're constantly chewing something, the environmental influences constantly shape. Someone have teeth, someone have braces, someone has

implants, someone has crowns or caps on it. So all of these are different things that influences your oral cavity. The same thing for the gut, right? So I think the understanding came in with the technology and how we were able to understand more and more. And as you pointed out, now we know that it's viral, murky, whatever it comes to the end, right? So I think we probably in 10 years and 20 years, we will probably know a lot more that we don't know now.

Dr. Mangalam

Yeah, thanks for setting it up. So I think I have been involved with this explosion and when all these like, Sukirth mentioned human microbiome project. So you know I am an immunologist by training when you are introducing. I did PhD in immunology and then I postdoc in immunology. So during my postdoc, I was working on this project where we have this gene in mouse, which is linked with multiple sclerosis class 2 gene. but not every mouse which have these genes get diseased. So it means there was something mission. So there was this concept coming up that there is a genetics and there is a environment. So we wanted to isolate, we were working with a GI guy, Joe Murray, who was in Iowa City, in fact, and he moved there. So he do lots of endoscopy. So we isolated lots of bacteria and gave it to mice. And it was a big failed experiment, like in science, it is all is. But in that, we found a whiff of a hint that certain bacteria can protect from disease. So that was my first foray into it. And in fact, finally, we introduced a concept called BRUG, which is bacteria as a drug that time. We patented that bacteria in 2007, in fact, and the same year Human Microbiome Project came. So when human microbiome project was announced, every medical institution wanted to get on that microbiome bandwagon. Luckily, I was at right place and right time because Mayo made a center for microbiome and they started some seed funding. So we got to involve in those projects very early on. And like Sukirth mentioned that this was the sequencing technology. And funny enough that all these came from soil microbiome because soil microbiome is where everything was standardized first. So then I was able to understand all the nitty gritty of sample collection because you learn from fail attempt more than anything. So when I came to Iowa, in fact, that's what helped me in establishing microbiome core, which helped not only our institute, but all over US people call me to get their sequencing done. And like Sukirth was saying, most of these studies, which is started in 2007, they were published in 2012 and 2013. To give you some prospective, in 2007, there were 300 or 400 publication in microbiome. And last year it was 36 or 37,000. That much it have exploded in last 10, 15 years. Wow.

Dr. Clancy

Well, the only thing I have to add is I was around before there was PCR. and had to do the old fashioned gel. So you wait three weeks and see what happens. So this is a podcast for,

in general clinicians. So from a clinician's perspective, what would you say the most important functions of a healthy microbiome are, especially in explaining it to patients?

Dr. Ganesan

That's a great question because I am a periodontist and the etiology of periodontal disease is dysbiotic microbiome with the susceptible host. That's an established definition of the disease, right? So I always say is, you know, at any given point of time, anybody in the oral cavity, they may have anywhere between 600 to 800 species in the bacteria in the oral cavity. And doesn't mean that we're all just brooding with infection, right? It's always the body knows, and we're born with the bacteria. So your body really knows when to throw a tantrum and when to get along with the bacteria. It's going to see certain bacteria, and in oral cavity, we call them like, you know, red complex, green complex, yellow complex, based on like how healthy or how they're associated with it. As you may understand, a red complex bacteria means that it's actually pretty bad, like Porphyromonas gingivalis. Treponema denticola, Tandrilla forsythia. So those are, your body knows that, okay, you know, if this bacteria shows up, it's bad because of the function. So as long as that marriage or the relationship between the mucosal surface that's inside of your cheeks in your claviculum, which is right around your teeth, below your gums, if that area is loaded with bacteria, but also has a lot of epithelial cells. So there's like a constant policing. As long as that interaction goes okay, I think you maintain health. So homeostasis is health. When that interaction goes wrong, that's when this dysbiosis comes in. It's the opposite of eubiosis, which is good and healthy and commensalism, but dysbiosis is bad. And that could be because of a lot of things. That could be because someone started smoking, someone is diabetic, someone has not seen the dentist in a long time and actually their oral hygiene is poor. So the abundance of the bacteria has increased. Or we are finding with more of our collaborations, and Ashu and I work for the past seven years almost on every grant, I want to say. And so it could be multiple sclerosis, it could be diabetes, it could be obesity, metabolic syndrome, cancer. So there are external factors, internal factors, all of this can change. So when I talk to the patient, I always say the goal is to make sure that interaction is remaining stable. Means you may have to go get your A1C under check. It means that you may have to make sure that you see your dentist every six months. There is a rough surface on the crown. Let's make sure it's not retentive for the bacteria. Let's make sure that it's actually in lower level. Our goal is to make sure that this interaction remains at a eubiotic stable level and we stay as that healthy homeostasis. If it's not, then we are looking at the whole dysregulated problem.

Dr. Mangalam

One way I try to explain gut micro, at least in the gut microbiome, is that use this framework called digest. And it goes, D stands for digest. So basically the first function we attribute to gut microbiota was that they digest food for us. And we can go into more detail that how we have evolved with that. But simplicity for their function, second I stand for, they instruct our immune system because immune training is one of the important functions we are learning. And then through all these metabolites, they guard our gut lining because we have to work with them, but also we have to keep them separated and they should not come inside our lumen. So we guard that lining. E, energize your body. I think we harvested these microbiota because they help us getting more energy from the same plant food because we didn't have enzyme. Unless you want a big body like elephant or giraffe, if you want to get away with that, you can use gut microbiota to extract more energy from that. Then S stands for signal because then they produce lots of these metabolite neurotransmitter or endocrine which can directly interact with your brain. And then overall, like Sukirth also mentioned, is that eubiosis are homeostasis. It means they tune our whole health. So this digest analogy, I wanted to use this framework to mention that that's how microbiota digest. They provide nutrients, they instruct our immune system, they provide energy to our body, lots of signals to our brain are neurotransmitter because we know that 90% of them like serotonin is produced in the gut and overall it lead to a healthy system.

Dr. Clancy

Those are great answers. Absolutely. And we started into it, but let's add a little bit more to that as far as really the microbiome physiology and how it works. So what else would you like to add as far as the role that the biome plays in regulating and setting up the immune system under normal conditions?

Dr. Mangalam

One thing analogy I think we have to do because we do lots of these early life gut microbiota and adult gut microbiota. So when we are born, we are born astral. In initial phases, when we are on a liquid-based diet, we have a very simple gut microbiome because milk is the only thing which have oligosaccharides. So we have bifido and lacto species because we don't need much. All the fun begin when we go from a liquid-based diet to a solid diet. which have lots of plant-based nutrients beside other complex things. And at that time, our microbiota expand exponentially. So what they do is because now you need them to digest this and produce lots of these metabolites. But as a immunologist, we know that, like Sukirth mentioned, anytime bacteria are microbes, it means something bad because they were associated with disease and that's what we learned first. So Then what happened is our body look at these guys and see, my God, means these are microbes. We need to fight against them. But then microbes tell, no, we are helping you. We are not the

bad guys. So this symbiosis, what we learn about the symbiosis, which happened where bacteria lower their immunostimulatory molecule and our immune system learn to live with them. And during this, what happened is that Bacteria also help our immune system to recognize them as their own, although they are foreign. So it means they induce this tolerogenic immune response. Regulatory T cell, it is known in germ-free mice. If you don't have gut microbiota, then you don't develop regulatory T cells. And lots of, I mean, that is just scratching the surface. And at the same time, It is also now known that there are certain bacteria which are responsible for inducing TH17 response, which is required for extracellular pathogen. And these are specific bacteria which can bind to epithelial layer. I don't want to go in too much detail, but you know, whole gut is not same. In the small intestine, you have a thin mucus layer because you need to absorb nutrient and exchange other things. So that's where the direct interaction between gut bacteria or microbiota and our host happen, where they can bind to epithelial cell and induce lots of these TH17 response. And so diet-induced allogenic response or T-reg develop in a small intestine. But in colon, we know that mucus layer is very thick, so bacteria cannot directly go to all these bacterial metabolites. What we always talk about, fiber, salt chain, fatty acid, as well as other metabolite. they can cross and activate regulatory T-cells. Putting it all together, they act like a tune so they can tune our immune response because we know that somebody can argue that you need thymus to induce all these T-cells and bone marrow for B-cell response. But what we are learning slowly is that gut microbiota tune up based on how it can go higher or it can go lower.

Dr. Ganesan

And actually, that's beautiful, Ashu, because I think we learn a lot from the gut microbiome perspective because the colonies and the functions. And the oral cavity, if you think about it, as I said, it's the start of the canal, but the GA tract is very different in terms of the environment. In applying the similar roles and conditions that Ashu was talking about, one of the big roles of the oral microbiome to maintain a healthy environment, and we call this, we learn a lot from ecology, from soil and ocean and It's called niche saturation. So it's an I explain this to the patient all the time too. And I say, if you have your lawn and if you want to make sure that you don't want much of the weeds in there, but you want to make sure that the lawn has all the grass and the plants that you actually want. And if you colonize your lawn with all of that, is minimal space for the weed. But the moment your actual lawn dies, then you're going to have a lot more of the weeds coming in. And imagine now the weeds are the bad bacteria and the lawn, the grass is actually a good bacteria. So as long as we keep the mucosal surfaces occupied with a healthy bacteria, so it's literally a fight for the space, right? So that's one way your bacteria actually helps the healthy bacteria. We call it either niche saturation or colonization resistance. So it doesn't just give you that. And it's

very similar, the same thing, you know, the moment the first tooth erupts in the oral cavity, you have the bacteria started forming all around. And the same concepts of immune tolerance and influencing the T-cell responses and even regulating the neutrophil traffic all happens in the mucosal surface in the mouth as well. And the same thing with epithelial integrity and all those things, right? One of the other factors is also when you talk about how do we maintain health is it kind of ties back to the previous question we talked about also, like how do you understand the bacteria and microbiome? The first questions we always ask is who is in there? And you know, and I threw out some bacteria names and Ashu threw out some bacteria names. All of this is telling us these kind of bacteria exist, right? Now, the health is not just presence or absence. It's about what they actually do. And bacteria is always like, if one highway is closed, you're going to take another highway to reach your destination. So if you lose some bacteria, the cool thing about living in as a community is someone can always sub in for you. So the bacteria will always find a way to find different functions. So that's when we started understanding what is metagenomics? What are the functions of this bacteria? And we actually go back and when I talk about this to my students, I always say, you need to go and read back your O-chem and your biochemistry because the functions are talking about your TCA cycle that we read in biochemistry. All of these will pop up and how energy efficient are these in the process? Now even more we're understanding just because the DNA has the potential to make these functions, it's not enough. We need to know what actually gets transcribed. So then we have to understand the transcriptomics. Then now we're identifying what does a healthy transcript look like. Now we are over all of that and we say, well, you can have these genes, you can have these transcripts of RNA produced, but the interaction will actually end up in the end products, which are the metabolites and the proteins. So we have come from understanding who is there to all the way what they are actually doing, how they change the phenotype to a leaky gut or a periodontal disease. It's based on what metabolite and what proteins are identified at the end, right? Now we are identifying some of the healthy metabolites. You know, when you say the short chain fatty acids, for example, the butyrates or the pyruvates, we see that is mostly associated with health when you compare to someone with obesity or someone with other diseases in the oral cavity. So definition of the health gets a lot more granular and more nuanced as we start understanding more and more in these days.

Dr. Clancy

This is fascinating. So let's talk a little bit about what factors then influence over time and influence the stability of it. What are kind of the top contenders as far as messing with the balance here?

Dr. Ganesan

I'll talk about the oral cavity clinically. There are studies to show that it could be the oral cavity, the oral microbiome could be influenced by very many number of factors. It could be some of them are intrinsic factors, it could be your ethnicity, it actually could be whether you brush your teeth how often, your oral hygiene, your local inflammation, whether there are even like studies to show whether there are changes happens, how often do you take your anti-inflammatory medications? Whether someone has diabetes or not, someone has their BMI and waist circumference increased, someone has a metabolic dysfunction, rheumatoid arthritis, someone has multiple sclerosis, there are studies to show Alzheimer's. So there are so many factors that can actually influence someone, whether they actually have an implant, you know, then their microbiome is different. Whether they get their cleanings done every six months versus one year versus never get to see a dentist. So all of these things can impact the oral microbiome. The implications are that all these factors can So we have to take care of those factors. But when you're thinking about a research study, then you have to control for all of these factors to understand the true impact of the microbiome in the cavity. There's a beautiful work actually that's based on the gut microbiome from Yasmin Belkade's group at NIH at the time talked about what are all the different factors that can affect in the gut. But of course, we don't have that kind of a study in the oral microbiome, but there's actually a lot more of these factors I mentioned affects the oral microbiome.

Dr. Mangalam

Let me get into more detail. And so microbiota, you can think about, they are metabolizing gait where everything we eat, drink, or even breathe, microbiota will interact with it because they are always looking for carbon source, nitrogen source, protein, fat, whatever they can get it. So what can influence is that external factor is that what we eat or drink. So that is one of the things which can affect them. Also our lifestyle. So external is whatever we put it in, but then also they are internal factor which depend on our lifestyle. So if we are a very active lifestyle, there are lots of studies which have shown that we have a very healthy and diverse microbiome. but at the same time, we are stressed or we are depressed, like Sukirth said, not a good oral hygiene habit, or we are eating a food which is not very healthy. So all these factors can influence, but it seems that diet has the biggest influence and it is going to be every time I say something. So as we talked about, like when there is a weaning from liquid to solid diet, the microbiome change because the diet change. And it is very dynamic, but Right now we are working on a project where we're seeing that genetics also play an important role in regulating gut microbiota. So host gene, external factor, and our lifestyle, those are the things which can affect our microbiota.

Dr. Clancy

So Sir Kate, you've mentioned the term dysbiosis several times. What does that mean clinically and what's happening biologically with dysbiosis?

Dr. Ganesan

Right, that's great. So when you think about dysbiosis, I think it's important to understand what is eubiosis, because it's a disruption of the normalcy. For example, in the dysbiosis is when that disruption of this normal host microbiome relationship, if you think about it, that results, because of disturbance, what happens is that there is a loss of beneficial functions. And probably as we talked about, the colonization resistance is lost. So which means there's an expansion of this potentially harmful organisms coming in. And there is, say, altered microbial activity. You know, if you look at the genomics, transcriptomics and all of that, at the end of the day, the phenotype changes. When we call about clinically a phenotype is you're moving from health into disease and into inflammation. So when I always people think about this, even including myself when I first started here, dysbiosis means that it's not just wrong bacteria or bad bacteria. It actually also includes the changes in the functions, in the metabolism, in the host interactions in all of these things. So clinically, when you think about when do you think a dysbiosis is happening, it could be increased susceptibility to infection, right? It could be some kind of a chronic inflammation. It could be an altered barrier function, like the barrier immunity that Ashu was talking about. In the oral cavity, it could be just, you lost all of this healthy bacteria in the gums, and now you have gingivitis and periodontitis because now it's an inflammation-associated biofilm. Or if you look about, your environment has changed so acidic, someone is drinking an acidic beverage all day and they have low secretion of saliva, then you're increasing that chances of getting caries for these patients. So which means you're going to have a lot more acidogenic bacteria and the same streptococcus, which could be good in the gingival environment, is bad on the caries environment. So then that's what we talk about at dysbiotic. And the best example clinically you think about in the gut environment is your C. diff infection. Everybody has heard about that. So clinically, what it means is that there's this complete overgrowth disruption and you have this harmful inflammatory organisms associated coming up. and you're losing the beneficial bacteria, the common cells.

Dr. Mangalam

I think we have talked about what is the healthy and we didn't go into detail, but what the Sukirth put this grass like your lawn, a very lush green lawn, and let me take you to the bigger like a forest ecosystem. What we do, because people generally think about gut

microbiome, they digest, you eat them fiber, and then you get charch and fatty acids. But like I mentioned a little bit, that fermentation substrate like fiber, resistant starch, fructooligosaccharides, they are just one part of the story which microbiome do. Other thing microbiota, like I mentioned, that they are metabolic gatekeeper. Everything we eat, they converge to like lots of bioconversion. One of the project in our lab we study is that how phytoestrogen in diet like soybean, which have phytoestrogen, how it is similar to estrogen, but you don't get full benefit of it until unless you have a specific bacteria to metabolize into a right metabolite like Equal from Digene, and then you get these effect. Similarly, they can metabolize drug, and we know every day these days we are seeing that They can make some drug better or some drug worst. And even in the case of alcohol, we know that some people can get the same higher alcohol level with the same drinking than other. They also do bile acid metabolism and some of the sukid work, they work on tryptophan, which is an important part of that. Protein, and we know fermentation in dolls is good in lots of cases, but TMAO, trimethylamine, I think lots of work from Steve Hagen group have shown that when you eat meat-based food, that choline and carotenine can be changed into these like TMAO, which can lead to atherosclerosis. And then there are non-nutritional modulator, polyphenol emulsifier, and all those things. So put it all together, there are lots of job these bacteria are doing. So if you take a small community in Iowa, there are lots of small community. For a community to function, you have a hospital, you have a school, you have a restaurant, then there are lots of communities. So let's say some physician left this community. Now there is a dysbiosis because this community is disturbed. But right now what we are doing is we are trying to find, let's say if Mike was there as a physician and we try to replace with another Mike, but maybe that another Mike is a chef. So when we are doing human study, we are looking at different community and we are trying to find bacteria, which is different, but Sukirth pointed to out that The bacterial name can change, but it does not matter who is there. That is the first step we are taking. But what is matter is what they are doing. So this biotic state is basically when this ecosystem, which is very well balanced, whatever you eat based on your microbiome, you have, you're putting healthy metabolite, you have intact gut. But Now this is disturbed by we talked about like diet, our healthy, our dietary habit or our lifestyle, which goes in out of whack, but that dysbiosis is compared to whatever that individual have. In a simple term, altered state, where now we don't have all the function, beneficial function, which I said that in the digest we had from these microbiota.

Dr. Clancy

All right, let's move over to what we know as far as links to diseases. And I certainly know that this is evolving as far as our understanding, but which disease states have the strongest evidence for contributory roles as far as microbiome?

Dr. Ganesan

That actually depends on the microbiome we're studying and the disease we are looking into, right? Because we have now clearly established that the body has different sets of the microbiome. And you talk about a C. diff infection, then you know that definitely a gut microbiome is out of the whack, right? It's crazy. And the same thing, if you think about in the oral cavity, if someone has cavities, so many cavities, or if someone has gum disease, 100% it's actually dysbiotic microbiome. That is the established etiology. Where the process is evolving and it's getting interesting is that in a lot of these autoimmune conditions like the multiple sclerosis or the chronic inflammatory conditions like what we consider even the lifestyle conditions like obesity or type 2 diabetes or even other chronic conditions like Alzheimer's or rheumatoid artery, those are where that we are actually looking into more of these conditions where that the role of the microbiome is we are trying to understand more and more of this. For example, In obesity and in metabolic syndrome, which we focus in our lab, there are studies to show because it ties back to what Ashu was talking about. You have a differential diet. We have studies to show that if you eat Mediterranean diet versus Western diet, your gut microbiome is altered. But when we do a control study and when we look at patients who are either patients with obesity or patients with metabolic syndrome, and we take out the confounding factor where that it is periodontal disease or the gum disease or the cavities, because we know that It is dysbiotic, right? So even when we look into the patients who have very good clinical oral health, but they are all either patients with obesity or metabolic syndrome, when we look at their oral microbiome, we find that their signatures look like the red complex bacteria we talked about. Their functions look like it's virulent. Their metabolites look like absence of these healthy metabolites and increase in all of these inflammatory metabolites. So kind of showing that this early dysbiotic shift, it preludes even the onset of some of these chronic conditions that can happen in the body. That's where the field is now evolving to see that if we can identify some of these bacteria and say, If some of these changes are signs in the microbiome, that could be a metabolite at the end product or a pathway, is this a precursor for the disease to start? are we, it's almost like, are we, it's like a Kennedy in the coal mine, like, are we able to see that even before the danger comes in? So some of the diseases is absolutely established. And if someone has, as I said, periodontitis, C. diff infection, caries, microbiome dysbiosis is the reason. severe pregnancy outcomes, adverse pregnancy outcomes. We know that the oral microbiome is dysbiotic in that environment. So clinically, more and more what we are thinking about is thinking in the next generation or the current clinicians to think about is that when you see someone who has the metabolic dysfunction or the chronic inflammatory conditions, think about what is going to happen in their microbiome too. Think about what their risk factors and their susceptibility to disease

is increased in these patients. And so that's something to think about and where the field is now.

Dr. Mangalam

I'll take this question in a different way. I think what happened in a medical field when we learn diseases, we always learn this Scott hypothesis. We take bacteria out, we put bacteria in, it means this bacteria is associated with disease. But microbiota and microbiome is little different because we are talking about this, like I tried to mention, this Holobiont system. So we are trying to say that, oh, this bacteria is associated with the disease or not. I'll say that every disease is associated because every day you take a news article or a journal article, it seems every disease is associated with that. And the way to put it is that Since these microbiome are part of this functioning machine we are, if they go out of whack, so the question is that, do they get out of whack first and then you get a disease? Or once you get a disease, they get out of whack. And I think the both are true. It is a circular argument. So Like Sukit mentioned, in acute diseases, it is very easy to study because there is no other thing like in C. diff infection is the best example, that 85% because you can do fecal microbiota transfer and then because this is a system which is dependent on not having that gut microbiota. But in chronic diseases, it is very difficult because first chronic diseases by name itself There is a genetic factor, there is an environmental factor, there is a lifestyle factor. For Ms. by the time they come to clinic, the disease have started long ago before that. So I think the right question to ask is that not what have the strongest association with the disease, because I think every time human have an adverse health event, microbiome is going to be involved because they are part of the system. I hope that makes sense.

Dr. Clancy

It very much does. And my field of psychiatry, a third of the patients I see with clinical depression do not respond to traditional treatments. And I've always had the belief that part of that is just the treatments that we have only cover two-thirds of kind of the dysfunction. There's another whole set of dysfunctions that the medications, the monoamines that we're working with that affect serotonin and dopamine and norepinephrine are just not what the issue is for these patients. it opens up this possibility that chronic treatment resistant diseases, there's an Ave. here as far as treatment that might be helpful to them. Do you see on the horizon any particular tough to treat diseases where you think maybe microbiome is playing a bigger factor than is getting the attention that it should right now? You mentioned Alzheimer's. Is there other big public health issues where microbiome needs to be at least considered as a contributory factor.

Dr. Mangalam

First thing is just like I mentioned, every disease, but where it is coming up as a very important factor is that, like you mentioned, when you treat these patients, only two-thirds respond. So what is coming up, at least in checkpoint inhibitor in cancer therapy, is that not everybody responds equal because nobody is taking care, like, okay, what is the microbiome? of these person, what is the baseline microbiome is? And I want to give an example of the study we did on microbiome with Terry Walz, who have this Walz diet or modified paleo diet. And what we did is that, although the sample set was small, but we found that if we look at the baseline microbiome of these community structure, we can predict that who is going to respond versus who don't respond because we already knew that who are responder and non-responder. And I think that is the issue because if you put any dietary and nutritional supplement and even drugs because we know that bacteria metabolize them, I think the future is that we need to have a baseline microbiome and understand the function, because sometimes just Sukit mentioned, and I also mentioned that who is there is the half the story. The full picture is who is there and what they are doing. So I think to get back to your question is that they are going to be involved with every disease, some sooner than later, depending on how complex they are, because we are just trying to understand these with the new technology, who is there and what they do with metabolite. Now we can do proteomics and transcriptomics. So I think they are going to be involved with everything.

Dr. Ganesan

And I think it's two big examples if you think about was, when I was doing my fellowship at the NADCR, my postdoctoral fellowship was focused on chronic graft-versus-host disease. And the chronic graft-versus-host disease happens in these bone marrow transplant patients. And it is considered this autoimmune, alloimmune kind of a condition, so people didn't really think about like a lot of the oral microbiome concept wasn't, that popular, when you think about the GVHD because you actually give them a full dose of cleaning the system with antibacterial, antifungal, antiviral even before you start the process for them, right? Actually, the studies back in the 70s actually showed in the pediatric population that when that microbiome is fully eliminated, it actually worked really well, based on the prevalence of redundant of the remaining bacteria, then they all actually had GVHD. And they showed it in the mouse too, like, in a sterile environment, in a, when you have no bacteria, there was no GVHD. The moment you actually introduced bacteria in the mice, that's when the bone marrow transplant mice developed GVHD. So this is just an example to show that how a lot of these experiments are very difficult to perform, right? having a sterile environment created, it's not easy to have these facilities even done through the

process. But this kind of shows that the significance of the microbiome, especially in certain diseases, as Ashu talked about, cancer, checkpoint inhibitors. Now our focus in the lab is on the cardiovascular diseases and obesity and metabolic syndrome. One clear role, production of nitrates. Everybody eats, spinach is good for you, beets is good for you, they are all nitrate-rich fruits. But the nitrate, you know, is absorbed into the bloodstream, but then they get secreted in the saliva. Then the conversion of that nitrate to the nitrite happens because of a lot of the oral bacteria that could be, you know, very common things like Actinomyces, Neisseria, Rothia, like these are very common commensals that are present. Then when this nitrate is swallowed, that's when it becomes nitric oxide. And nitric oxide is very important. We all know the medical implications of nitric oxide for vasodilation, for the endothelial functions, for lowering the blood pressure because of the vasodilating effect. So those are some of these chronic conditions that we are actually feeling that the oral microbiome and the functions of the oral microbiome is going to be a lot more critical in the future years. Because there'll be no nitrate production if you don't have any of these bacteria. You can have all the spinach and all the beets and celery we want, but we do need the microbiome to get this effect.

Dr. Clancy

I'm starting to see a way of explaining this to other physicians as well. I staff the emergency room. We have to do a fair amount of screening labs for a patient to be stable enough to go to the psychiatry unit. We look at hydration status, we look at electrolytes, we look at kidney function, we look at liver function, and I'm seeing kind of on the horizon your biome status as well is going to be one of those things that needs to be on the checklist. So let's change gears again and talk about diet. As you mentioned that diet is a huge modifiable factor. What is your advice as far as diet, as far as fiber, as far as a specific Western diet, Mediterranean diet, what happens when you go weigh keto? What are you seeing and what are you learning about diet that is good and diet that is not good?

Dr. Mangalam

So this is a topic very close to my heart because diet is the biggest influencer, but not every diet is same. So since you mentioned two diet, let me get into detail about Mediterranean diet and keto diet. They have a different way they act. Mediterranean diet, one way I always say is that keep your microbiome healthy is that eat lots of different variety of food, not just eat lots of fiber because that's a misconception, I think it is in the field. So Mediterranean diet or any plant-based diet, when you take it, will be modulating your gut microbiota, trying to make it to more harmonious or a healthy gut microbiota. Keto diet is a little different. Keto diet does not act on your microbiota. It works on your host endocrine system or host physiology to change that physiology, which can indirectly affect it. So keto diet have a

different effect than Mediterranean diet. And since we are talking about microbiome, I think If I have to promote, I will promote more a Mediterranean diet or a variety of diet, but I haven't worked in keto. But the mechanism through keto act and lots of these diets I've seen is that for short term, they are good because you induce lots of cortisol because you're putting your body under loss of stress. So in short term, they might be good, but in long term, I don't know. But plant-based diet, Mediterranean, which have data from thousands of years of people eating it, is, I think, better to at least grow your microbiome to a healthy state.

Dr. Clancy

Sukirth, how about you? Advice on diet. But let's go beyond sugar being bad.

Dr. Ganesan

I think Ashu put beautifully, like, you know, I think the best microbiome diet is not just like a single diet. It's, as we all know, minimally processed and make sure that it's a lot more fruits and vegetables and the legumes and the Mediterranean, you can call it Mediterranean, you can call it like the whole food diet, but it's important to, and again, not all fat is bad, like healthy fat is good. So that's the most important part to keep in mind, minimizing the ultra processed. And there is a difficulty in studying the probiotic or the prebiotic supplements. That's another big thing that people talk about. And it's very difficult to do a randomized clinical trial and to see whether these effects are have. But if you think about in the past or in the ancient times how people have had food and different cultures, talk about how important and significant is the fermented food. So that is also something that will be actually helpful for your gut health or your oral health or the microbiome health. It could be like a kefir for the yogurt or kimchi or those kind of food which are traditionally fermented. That is also pretty good for your health of your microbiome. And then as you rightly said, the oral cavity is the beginning of your gut tract. All these things will start from the oral cavity. So healthy oral cavity means healthy body, which means it's healthy gut.

Dr. Mangalam

I just want to add something on that. So I have an acronym for this same concept called PLANT, plant diversity. eat lots of that. Live cultures, like Sukirth was talking about fermented food daily. In fact, I believe that fermented food is better than probiotic in the sense because not only they provide live bacteria, but because live bacteria are also producing lots of these metabolites and also they can train immune system. And there's a study which came in last five years from Sonnenberg Group, Justin Sonnen Group, that fermented food was better in having a more diverse microbiome and reduce inflammatory metabolite.

Dr. Clancy

Great. You know, we just did a podcast on ultra-processed foods and this just feeds into it so nicely as far as just throwing in all those foreign toxins and well, how it can just disrupt, disrupt, disrupt. Yeah.

Dr. Ganesan

And what's interesting was thinking about growing up in a, I'm A South Indian origin and I grew up in a South Indian family. And we have this fermented rice that's actually made the day before. And it was considered to be a punishment that my mom would make me eat that. And I hate this and it's a little sour and I don't want that. And now it's interesting to see that how diet that's added with the yogurt to it. And anytime, and if I say I have a tummy ache, I want to go to school, like my mom would say, well, you're going to eat that fermented rice with the yogurt. And believe it or not, in a couple hours, at the end of the day, you actually are fine. But now that's what we're going back to. And we didn't, I don't think at the time we thought about the scientific reason for it. But one of the things I always tell my patients is, Just because you started supplement and you're taking antibiotics today and you started your supplement today, it's not going to work. It's about practice, doing it long enough, consistency, and I think that's also something to keep in mind with the dietary habits.

Dr. Mangalam

Yeah, and I just wanted to add because I read in plant, I said plant diversity, life culture, but A is for antibiotic, judicious use of that, N is nourish the whole person, sleep, stress, movement, and T is for trim ultra-processed food. And another point which Sukirth was saying, and I was reading about it is so interesting. So you know, if you boil potato and eat it right away, or you make a rice and eat it right away, it is not as nutritious if you put it and make it cold. Because then all these registered starch, I think the way they get in, they then get digested in stomach because stomach can alpha bond, it can break. But because of this cold, they go into colon where you get more out of these cold things, like same way rice next day, potatoes again, cold pasta, they give you more benefit than a warm food.

Dr. Clancy

Yeah, absolutely. Absolutely. So our general population, our patients are bombarded with advertisements as far as probiotics and prebiotics and such. Do you see them as healthy or is there a simpler alternative? And you've already told us about what that simpler alternative is.

Dr. Mangalam

What I will say is that probiotic in a limited, only places I have seen it work in a very acute setting. So probiotic might work in maybe C. diff are. One study I was in a probiotic meeting, which was in Mexico where Patient undergoing surgery, they found that they look for certain fatty acid in LPS, and then they found that hospital stay and post-surgery infection was lower. But other than that, probiotic as a supplement and as a disease medicine, I am not a big fan of it. Prebiotic, if I have to choose between two, I will take prebiotic because it will expand the good bacteria you want to expand. So prebiotic, I will choose over that. But I think synbiotic is a better option. So think about this is that there's an orchestra and music is out of whack. Even if you take a Mozart and put it there, like the best probiotic you can think about, it is very difficult because everything is out of whack and how you can fix just putting one good person in there. So what you need to do is that a synbiotic means you put it what the bacteria feed on and with the bacteria and the food source together. And then if you give, I think you have a better chance. And in fact, we are developing something with Ali Salem here that putting a phytoestrogen with phytoestrogen metabolizing bacteria, because in our animal model we found that diet don't work if there is not right bacteria for it to metabolize these compounds. So for me, prebiotic, sybiotic, any day over probiotic.

Dr. Ganesan

Exactly. When people think about these yogurts and they have this probiotic added to it, please pay attention to the number of sugar that is in there too. Like it has 30 grams of sugar and they add all of this bacteria to it. And it's going to definitely mess your microbiome when you add so much 30 grams of added sugar to it, right? And building the base is what the prebiotic does. And in my mind, when I eat a banana and oatmeal, I already am taking enough prebiotics in my body. You don't have to search for these supplements. And for probiotics, when someone is on a, as Ashu said, a long-term antibiotic for a specific medical reason, then sure, at that point, it's more of like making sure that you are not destroying everything and you are on a 30 days of a Z-Pak or something that's going to destroy your system. Absolutely. And if you have not done that before, then it's more of an acute prescription kind of a thing. But I think it's just building the system and the building the system happens with laying the platform and that happens with prebiotic.

Dr. Clancy

Any other examples of good prebiotics and any other good examples of symbiotics?

Dr. Mangalam

Again, I think it is a very boring answer every time I give these talks, but same the plant analogy. Use, eat lots of diverse food because if you're taking prebiotic for something, you are just filling one niche about fiber, let's say. But like I talked about, there is fiber, there is so many bioactive molecule because bacteria are just converter. They convert all these food sources into these betabolite, amino acid, fat, everything you eat, they convert it to something useful. Like I said, it is very boring answer and most probably our parents told us to do when we were very young, we never listened to them. But having a healthy lifestyle, eating diverse set of plant food, avoiding ultra-processed food, I think in your last episode I heard a lot about it. So I think those are the things I will advise.

Dr. Ganesan

I think for the prebiotic examples to add on to that, I would say, as I said, banana, oats are great to feed that. People talk about even a lot of the green leafy vegetables like the leeks or, you know, a lot of the times the differentiation between the prebiotic and the probiotic gets lost. And people don't realize, I think that the key point to take away is that prebiotic is setting the stage. It's not replenishing anything. It's making sure that you have a good, healthy bed where you have the good, healthy bacteria grow. Probiotic is only a, you know, you're in the hospital and you have an IV antibiotics and you need to restore your system. That's when the prescription probiotic comes in for you to take it like an acute phase. But the prebiotic is, all these natural foods and it's not as sexy to talk about, right? It's just your everyday grocery shopping.

Dr. Clancy

Well, I was talked into a probiotic once and I didn't feel good an hour afterwards and so never again. So there was something going on, but it just didn't feel right at all. So just kind of a side question because again, our patients are in a world where a lot of things are being marketed to them. Do you guys see a role for microbiome testing today or in the future?

Dr. Mangalam

I will say in future, yes. Once, and I will give you a very funny example. I don't know if you heard Flash Forward, a podcast which used to come, we talk about the future. This podcast, what they say that a patient go to a doctor, doctor get his microbiome, metabolome and proteomics maybe. and then open his cabinet, he said, okay, these are the thing which are missing metabolite function. You take these, I will not say probiotic, but drugs because then a specific bacteria or metabolite function, which is lacking, you take it. So yes, right now, no, because what everybody is trying to do is look for a name, bacteria name. which is not right. Like Sukirth mentioned, it does not matter who is there, but what they do. At the same time, people are looking who is there, not what communities are

there. So we have developed some method where we look at the community structure rather than individual bacteria. So I'm hoping that in future we will have when we understand it better.

Dr. Clancy

Great, great. So let's finish this up with some practical takeaways. And you've done a great job of this, but I just want to circle back again. What do you think are the most practical, evidence-based, microbiome-related recommendations that a physician should have as far as a conversation with a patient? And I remember digest and I remember plant.

Dr. Ganesan

Absolutely. The microbiome is actually just part of your normal human physiology. Don't think about microbiome as bad. So they're not just pathogens. They are important for maintaining health. So I would want to make sure that we all understand that the microbiome is also good and it's important to maintain the balance, the relationship with them. And this comes in as a dentist that oral health, oral microbiome is related to overall health and the gut microbiome health. So we can't extrapolate the information from the gut to say we have understood enough, we don't need to, you know, get neglected. There is already enough separation that has happened between the oral health and overall health. So I think this is another reason to go back and think that what starts in the oral cavity ends up in the gut. So I think it's the takeaway is that the oral microbiome, gut microbiome, those health are important. I would say be very judicious on the use of antibiotics. We don't have very many new antibiotics developed in the last decade. So you have to keep in mind that we don't overuse them and end up with antibiotic resistance and lose actually the potential help with that. And one thing talking about is that I don't want to oversell anything as much as I'm a proud microbiome PhD scientist working on all of that. At this time, we have a lot more description studies for the microbiome. But we want to make sure that we understand all of this better. There's a holistic approach to a lot of these things. But we're not there yet to say, I'm going to prescribe you a parforma or gingivalis testing. I'm going to prescribe you Akkermansia testing. And if your levels are lower, which means you go and your risk for this, we're not there yet, right? We are still understanding a lot of these things. So think about the prebiotics more, get some healthy food, diverse food, avoid sugar, see your dentist, and sometimes, you know, the oral health appears much before the systemic complications occur. So those are my few takeaways for folks to think about.

Dr. Mangalam

Hashu, how about you? Keeping your microbiome healthy, using that plant analogy, is that diverse? 30 species a week, I think that's what that human gut project have suggested that

they saw that if you eat 30 different kind of plant-based food in a week, life culture like yogurt, kefir, whatever you think, but at the same time, What work for a same person in the house or in your community? Don't take it granted because everybody is different. So eat something if it helps, like you said, you took probiotic, you didn't like it, so you move away from it. So anytime you start something new, which is not part of your normal lifestyle or food, just test this little bit before saying yes. If it is not working, maybe try different kind of life culture. Sukirth already mentioned antibiotics, judicious, or any drugs, I think it is very judicious use. Treat your body as a whole person, but like Sukirth also mentioned in different ways that there is no short-term fix. You have to work every day to make that, sure that you have a healthy community. Try to avoid or trim ultra-processed food as much possible. And at the end of the day, microbiome is not answer to everything, but it is very important because there is a human genetics and there is a microbiome. There are lots of environmental factors, but keeping your microbiome healthy at least have been shown so far that help you have a better lifestyle. And watch out for this space. Maybe we will have another podcast where we'll say we found a microbiome profile maybe in 10 years. And I just want to leave this thing is that people always ask that, oh, we are hearing about microbiome from so long and I'm tired of it. Think about all those like checkpoint inhibitor. They came in 90s. And by 2000, if you tell somebody, PDP, oh, I am hearing it from. So in medicine, I think you have seen it more than me or Sukirth that it take at least two decades, some time for things to get, means now things get it faster because we got technology which improve every day. But I think future is there, but we are going to be there, I am hoping in 10 years, but we never know.

Dr. Clancy

It does take a long time to move this battleship that is how we deliver healthcare. Absolutely. One more personal question. What is 1 microbiome related habit or principle that you personally practice in your own life based on the sciences as far as what you know?

Dr. Mangalam

One thing which I have done every time I eat lunch, I will go into food karma for 20 minutes or something like that. So one thing I started eating salad. So like practice what you preach. From last three, four months, I'm eating salad for lunch, taking my lunch 12 to 1, by 5 to 6, I don't feel hungry. Like appetite there to eat something else. And also clinically, because I just have my annual test and it seems that lots of things which were like borderline have gone to better size. And my Apple Watch told me other day that in last three months, your resting heart rate has got lower. So I don't know, but at least for N is equal to 1, I found that this salad-based lunch had helped me a lot.

Dr. Clancy

Sukirth, how about you? I know about oats and bananas, so.

Dr. Ganesan

That's my breakfast every day. You know, I'm A vegetarian, so I don't eat meat. I do have to think about diversifying my plant-based diet A lot. So I think, you know, it's a lot of different kind of plant-based meal, legumes and beans and carrots. So it's very, the diverse diet that I eat, I think that's something which I do. And the other thing is being a dentist and a periodontist, I make sure that there is no accumulation of plaque. And I see my hygienist every six months.

Dr. Clancy

Great. Well, I'll add my one thing as well. After we did the ultra-processed food podcast recording, one of the pieces of advice was just try to take it down a notch as far as ultra-processed foods. And I've been able to take it down a ton. And like you, Ashu, it is really different as far as hunger swings and such like that. Just getting that stuff out of the way is just, because those foods are designed to promote you eating more. you both have been great. And just thank you so much for joining us today and for your great work on the microbiome and the links of diet on overall health and disease prevention and disease modification. Just terrific. Our listeners, thank you for joining us for this session of Rounding at Iowa. And you can access show notes and instructions for CDUs and CME credits in the show notes. And we hope you join us again for another episode of Rounding at Iowa.